University of Alberta

Effect of Physical Fitness and Gender on Arterial Compliance in Adolescents

by

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requirements for the degree of **Master of Science**

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DEDICATION

I would like to dedicate this thesis to my parents, Nancy and Dimitrios Oreopoulos, whose continual love, wisdom and support have helped me through this process. You reminded me of the value of perseverance, hard work, and a positive outlook when I most needed it. You are truly inspirations for me. I would like to express my deepest gratitude to my supervisor, Mark Haykowsky. I have grown as a person, student and researcher because of your teaching and guidance. Thank-you for the time you spent assisting me and your words of encouragement. I am privileged to have had the opportunity to learn from you. I am also very appreciative for the help provided by my committee members, Richard Lewanczuk and Rob Welsh. Thank-you for your knowledge and resources. Finally, I would like to thank my husband and best friend, Mark Dueck. I am very grateful for your patience, kindness and humour.

ABSTRACT

The effect that physical fitness and gender have on arterial compliance in adolescents is not well known. The aim of this thesis was to determine the effect of physical fitness and gender on arterial compliance in adolescents. Adolescents (n=247) between the ages of 13 and 17 years were grouped into four fitness quartiles based on a Legér 20m shuttle run score. Large (C1) and small (C2) artery compliance were assessed using diastolic pulse wave analysis of the radial artery. Adolescents in the lowest fitness quartile had a 10% lower C2 compared to adolescents in the highest fitness quartile (p=0.08). In addition, shuttle run score was an independent predictor of both C1 and C2. C2 was significantly higher in males than in females, however, after controlling for differences in anthropometric, hemodynamic and physical fitness measures, the gender difference no longer existed. Vascular function may be affected by physical fitness at an early age. Increased physical fitness is associated with enhanced small artery compliance in 13-17 year-olds.

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CHAPTER 1

1.1 Introduction

Cardiovascular disease (CVD) is the leading cause of death and disability in developed countries [1]. Most cardiovascular morbidity and mortality can be directly related to vascular events including acute myocardial infarction and stroke. The major independent risk factors for CVD include an abnormal lipid profile (high low-density lipoprotein cholesterol and a low high density lipoprotein cholesterol), obesity, smoking, hypertension, diabetes mellitus, physical inactivity and advanced age [2]. Since a number of these risk factors are modifiable, primary prevention strategies focus on identification of these individuals and subsequent modification of risk factors.

Throughout the lifespan there is a slow but progressive accumulation of atherosclerotic plaques in coronary arteries [2] which become a risk factor for future cardiovascular events. Previous investigations examining the cardiovascular risk profile in humans have focused primarily on adults. Accordingly, the CVD risk profile in children and adolescents is not well known. Cardiovascular disease presents clinically in adulthood, however the insidious process of atherosclerosis begins early in childhood. The first visible stage of atherosclerosis (i.e. fatty streaks) can appear in the coronary arteries as early as 3 years of age [3]. Further, fibrous plaque lesions (the second stage of atherosclerosis) have been found in 20% of aortas and between 5 and 10% of coronary arteries of children between 2 and 15 years of age [4]. Findings from the Bogalusa Heart Study [5] reveal the extent of these lesions increases with age, and is directly related to all cardiovascular risk factors. In addition, a higher total number of conventional risk factors in childhood is significantly associated with a greater degree

of vascular involvement in adulthood. This suggests that exposure to risk factors in early life may have long-term influences on vascular health.

Recently, non-invasive methods have been developed to assess vascular function. Changes in arterial compliance precede the development of atherosclerosis and overt hypertension [6] suggesting the presence of early vascular disease. In adults, decreased arterial compliance is associated with all major risk factors of CVD [7-12], however, this relationship has not been well studied in children. This is an important topic of research because diseases including type II diabetes [13], hypercholesterolemia [14] and hypertension [14] that were once thought of as "adult-onset" diseases are now becoming quite prevalent in children and adolescents. Currently, children and adolescents adhere to a more sedentary lifestyle. Specifically, a greater reliance on parents to drive for transportation and less on walking or bicycling; computers, video games and television watching are more popular pastimes than active play, with some children spending 24 hours or more sitting in front of the television alone in a week [15]. The increase in childhood obesity also suggests an imbalance in both energy intake and expenditure. In a Canadian study, only half of youth between 6 and 17 years participate in physical education classes three or more days a week at school and only 17% have daily physical education [16]. Participation in organized athletics also diminishes greatly after age 13 in both genders [16]. Of note, children who report no physical education class during school are less active overall compared to those who do not take physical education classes [17]. Although physical activity levels decline in both genders, it is a very important problem in young women. The effect of certain lifestyle choices in childhood should be an important focus of cardiovascular research,

as a number of follow-up studies have demonstrated that children and adolescents with persistent high blood pressure are at increased risk for becoming hypertensive adults [18,19], and that physical activity, physical fitness as well as obesity tend to track from childhood into adulthood [20-22].

There are clear gender differences in levels of participation in physical activity. Once physical education becomes an optional subject, enrolment in physical education tends to decrease significantly, with the decrease more noticeable in adolescent females than males [23]. Adolescent males are consistently more fit, physically active and less fat than adolescent females [17,24-27]. There is also evidence that the gender difference in physical activity patterns may begin as early as three years of age [28]. Determining the impact of gender on vascular function will also allow us to determine any increased risk of inactive females.

1.2 Statement of the Problem and Purpose of the Thesis

Physical inactivity and low levels of aerobic fitness are known to be associated with obesity [29], hypertension [30], insulin resistance [31], higher lipid levels [32], tendency to smoke [33], and contribute to increased risk of cardiovascular morbidity and mortality [34-36]. Vascular function is strongly influenced by CVD risk factors in adults, however, the impact of physical inactivity on arterial compliance has not been explored in adolescents. In adults, favorable changes in arterial compliance have been demonstrated with increased levels of fitness [9,37]. Even leisure-time physical activity [38] and vigorous work activity [39] have been shown to have a positive effect on arterial compliance. Much of the research involving risk of CVD and physical inactivity has been limited to the middle-aged adult population, however, since

atherosclerosis is a progressive disease with its first manifestations beginning in childhood and adolescence, risk factors for CVD need to be evaluated in youth. Measurement of functional and structural arterial characteristics in adolescence may greatly enhance our insight into causes, development and pathophysiological mechanisms of CVD.

The primary objective of this investigation is to assess vascular function and physical fitness in males and females between 13 and 17 years of age. A secondary objective is to examine the influence of gender on vascular function.

1.3 Hypotheses

The primary null hypothesis is that there will be no association between vascular function and physical fitness. A secondary null hypothesis is that gender will not have an effect on vascular function.

1.4 Definition of Terms

1. Atherosclerosis – A slow, inflammatory process in which lipid deposits and fibrous tissue on the arterial surface progress to form plaques that may reduce blood flow or induce blood clots that can block flow entirely [40]
2. Arterial Compliance – A measure of the storage capacity of the arteries, or change in volume of an artery for a given change in pressure [41].
3. Sedentary – Individuals who do not meet the recommended amount of physical activity (i.e. 30 minutes of moderate intensity physical activity on most, if not all days of the week [42]).

4. Endothelium – A thin layer of cells that lines the interior surface of blood vessels and are involved in vasoconstriction and vasodilation, the control of blood pressure and blood clotting.
5. Endothelial Dysfunction - The loss of proper endothelial function and a marker for vascular diseases, often leading to atherosclerosis.
6. Vascular remodeling - The ability of the vessel to change its structure whereby the entire vessel becomes smaller. Changes can include thickening of the vessel wall and rearrangement or replacement of the vessel wall components [43].
7. Distensibility - Used to describe compliance relative to the initial diameter of a vessel [44].
8. Diastolic Pulse Wave Analysis – Analysis of the diastolic decay portion of a pressure wave.
9. Modified Windkessel Model – A third order electrical model with two capacitance elements (C1 and C2), an inertance element (L) and a resistance element (R), used to represent components of the human arterial system [45].
10. Applanation Tonometry – The applanation method is a measurement of the force required to flatten a certain area [46]. A tonometer is a sensor with a flat pressure transducer that converts the mechanical movement of the blood vessel into measurable electrical energy.
11. Large Artery (Capacitative) Compliance (C1) – Compliance of the large arteries, largely dependent on changes in pressure [41].
12. Small Artery (Oscillatory) Compliance (C2) – Compliance of the microscopic arteries and arterioles, largely dependent on the structure and function of the artery

itself. C2 primarily influences the frequency and rate of decay of the oscillatory pressure waves that originate at reflecting sites in the small arteries [47].

13. Flow-mediated Dilation – Vasodilation and change in arterial diameter after temporary occlusion.
14. Peak Aerobic Power – The amount of oxygen consumed during peak aerobic exercise.
15. Legér Shuttle Run – a measure of peak aerobic fitness involving running back and forth between two cones placed 20m apart.

1.5 Delimitations

1. This study was restricted to students from the Black Gold School District.
2. The sample consisted of 247 male and female subjects between 13 and 17 years of age.
3. Vascular function was measured by arterial compliance using diastolic pulse wave analysis with applanation tonometry of the radial artery.
4. Physical fitness was assessed by a modified Legér 20m shuttle run test.

1.6 Limitations

1. The subjects were volunteers.
2. The degree to which the sample population represents the normal population of adolescent males and females aged 13 to 17 years.
3. The degree to which the fitness quartiles represent distinct functional fitness levels.

1.7 Significance of this Study

Currently, the effect that physical fitness has on arterial compliance in younger males and females is not well known. Also, the effect of gender on arterial compliance

in this age group is unknown. This study will determine if reduced levels of physical fitness are associated with impaired arterial compliance in adolescents.

CHAPTER 2

LITERATURE REVIEW

This section reviews the literature related to: 1) the pathophysiology of atherosclerosis and vascular remodeling; 2) the role of the arterial system; 3) arterial compliance and its measurement; 4) impact of physical inactivity on CVD and vascular function, and 5) gender differences in physical activity and fitness patterns and its effect on vascular function.

2.1 Pathogenesis of Atherosclerosis

The primary underlying disease process that leads to CVD is atherosclerosis, often referred to as "hardening of the arteries". Atherosclerosis is a slow, inflammatory process in which lipid deposits and fibrous tissue on the arterial surface progress to form plaques that may reduce blood flow or induce blood clots that can block flow entirely [40]. The role of blood pressure in the process of atherosclerosis is not completely known, although elevated blood pressure may be involved in both the initiation (as a risk factor) and acceleration (as a risk contributor) of the atherosclerotic process. Atherosclerosis frequently involves the development of fibrous plaques the coronary and cerebral vessels, leading to myocardial infarction and stroke, however can produce changes in the peripheral arteries as well. Atherosclerosis begins in childhood with deposits of lipids and proliferation of smooth muscle cells located in the inner layer of the large arteries to form fatty streaks. In young adults, some fatty streaks may progress to become fibrous plaques when lipids accumulate and a fibrous cap forms above the intima. In adulthood, fibrous plaques continue to progress into complex lesions. Clinical signs and symptoms of the disease do not manifest until blood flow is

compromised either by vessel narrowing or plaque rupture and clot formation, leading to clinical events. It is generally believed that atherosclerosis represents a vascular injury process, and can be accelerated by the persistence of risk factors [48].

2.2 Vascular Remodeling

Vascular remodeling is defined as the ability of the vessel to change its structure. It is a process in which the vessel lumen becomes smaller due to thickening of the vessel wall and rearrangement or replacement of the vessel wall components [43]. These changes can be a result of risk factors or disease, neurohormonal influences (i.e. the rennin-angiotensin system) or aging. With aging, there is a thinning and fracturing of elastin and increased collagen deposition due to cyclic stretching of the smooth muscle cells, resulting in increased wall thickness [49] The physiological responses to pressure overload and injury are similar to those associated with the remodeling of the left ventricle [50]. For example, an increase in blood pressure can trigger adaptive smooth muscle hypertrophy such that the vessel wall thickness increases in relation to the lumen diameter.

The arterial wall has three layers: the intimia (innermost), media, and adventitia [40]. A single layer of endothelial cells line the intimal layer. The media is composed of vascular smooth muscle cells, surrounded by collagen and elastin proteins. The elastin forms concentric rings within the vessel wall. The adventitia consists primarily of connective tissue, with interspersed fibroblasts and smooth muscle cells. Endothelial dysfunction is believed to be one of the earliest events in atherosclerosis. The normal endothelium is a single layer of cells lining all muscular arteries which has anticoagulant and anti-inflammatory properties that help maintain blood in its fluid state

and provide a relatively impermeable barrier. It also plays an important role in vascular homeostasis, maintaining the balance between vasoconstriction and vasodilation. Endothelial injury is triggered by all risk factors associated with CVD, the most widely studied being blood pressure and lipid levels. It is manifested by a decrease in vasodilation through altered release of nitric oxide (a vasodilator) and angiotensin-II (a vasoconstrictor), as well as interference with normal clotting function [51]. Although these functional changes are designed to help maintain vascular integrity, if the injury process is repeated, the response is ongoing, leading to structural changes such as increased stiffness of the arterial wall due to hemodynamic stress and/or the endothelium no longer providing an effective barrier to low density lipoprotein (LDL).

The unregulated uptake of LDL results in development of large foam cells that accumulate in the intima to form fatty streaks. The transition from fatty streaks to fibrous plaques involves migration of smooth muscle cells into the endothelial space. As the structural heterogeneity of blood vessels is affected, thickening or remodeling occurs by vascular smooth muscle hypertrophy, accelerated breakdown of elastin and an increase in collagen fibers [52,53]. The eventual decrease in elastin which provides the elasticity of the arteries, and increase in collagen fibers which provide the tensile strength against the pressure of blood, produce stiffer arteries. The resulting endothelial dysfunction leads to a reduced bioactivity of nitric oxide, causing reduced vasodilation or even vasoconstriction, which in turn increases systemic resistance and raises blood pressure. The rise in blood pressure further damages the endothelium, setting up a vicious cycle. Ultimately, these changes in the arterial wall can predispose the vessel to atherosclerosis and plaque formation with resultant clinical events.

Impaired endothelial function has been shown in adults with established coronary heart disease [54], and the extent of endothelial dysfunction is linked with the number of traditional risk factors [55], suggesting that combined risk factors or persistent injury results in greater dysfunction. With prolonged arterial stiffness, the resulting increase in hemodynamic load can also stimulate ventricular adaptive changes. This may lead to concentric ventricular hypertrophy (increased wall thickness and mass), an important independent risk factor for cardiovascular death [56] or heart failure [57].

2.3 The Role of the Arterial System as a Pressure Reservoir

The systemic arterial system links the left ventricle to the peripheral circulation and acts as a conduit and as a cushion [58]. As a conduit, the arteries deliver blood to the periphery of the body in various proportions to the systemic organs through a parallel arrangement of vessels branching out from the aorta. As a cushion, the arteries play an important role in buffering the changes in pulsatile pressure caused by ventricular ejection. As the heart pumps blood into the arteries during ventricular systole, a greater volume of blood enters the arteries from the heart than leaves them to flow into smaller vessels downstream, because the smaller vessels have a greater resistance to flow [59]. The artery's elasticity enables them to act as an elastic reservoir, expanding to temporarily hold this excess volume of ejected blood, storing some of the pressure energy imparted by cardiac contraction in their stretched walls. When the heart relaxes, the stretched arterial walls passively recoil, pushing the excess blood contained in the arteries into the vessels downstream, ensuring continued blood flow to the tissues when the heart is relaxing.

Blood pressure depends on the volume of blood stored and the compliance in response to the left ventricle ejecting the stroke volume and subsequent relaxation. When the left ventricle ejects blood through a non-compliant large artery, a rise in systolic pressure occurs and is often accompanied by a decrease in diastolic pressure, resulting in a widened arterial pulse pressure. Clinical studies have confirmed the importance of a widened pulse pressure, in that increases are significantly related to an increase in the size and work of the heart [60], atherosclerosis [61] and are a predictor of cardiovascular mortality in both hypertensive and normotensive subjects [62]. Atherosclerosis often occurs in arteries where pressure and pulsatile stresses are high and is more severe in arteries that are poorly supported by surrounding muscle [61]. Stiffer arteries are more susceptible to injury by pulsatile pressure by causing small tears in the intima [63]. The stretching of the arterial wall i.e. by pressure, augments the endothelial surface area, increasing permeability to lipoproteins and adherence of leukocytes [64]. Therefore, in increase in arterial stiffness, along with hyperlipdemia or hypertension will accentuate the vascular aging process and may be a precursor to atherosclerosis.

Age- and disease-related changes in the vascular system are not confined to the large arteries but involve the small arteries as well [10,65-67]. Functional and structural changes in the arterial walls of small arteries precede and accompany overt hypertension and atherosclerosis [6,10]. Early return of reflected waves to the heart reflect changes in the structure of the arteries, and has been shown to independently predict cardiovascular risk [68,69].

2.4 Arterial Compliance

The blood vessels can be thought of as a series of three components that differ in structure and function: conduit arteries, reflecting sites and arterioles. The large conduit arteries, which are lined with elastin and collagen, are elastic and very dependent on pressure [41]. The elastin fibers absorb tension at low pressures, while at higher pressures the tension is absorbed by the more rigid collagen fibers [44]. Therefore, the higher the blood pressure, the greater the amount of collagen deposited due to remodeling and the greater the reduction in arterial compliance. The conduit vessels have a capacitor function because they distend during systole and recoil during diastole, in response to pressure changes in the vascular system. Therefore, the compliance of these large arteries can be defined as a change in volume for any given change in pressure [41], and is related to the change in diameter of the vessel following left ventricular ejection. Distensibility is used to describe compliance relative to the initial diameter of a vessel [44]. A loss of arterial elasticity leads to reduced arterial compliance and distensibility which decreases non-linearly with an increase in pressure [70]. Therefore, as blood pressure increases, a point is reached at which much less distensibility occurs at higher pressures.

As the large blood vessels branch and taper, there are reflecting sites where oscillations or reflections in blood flow occur, with endothelium and underlying vascular smooth muscle playing major roles in inducing these oscillations. In contrast to the conduit arteries, elasticity of the reflecting sites, which do not contain as much collagen, is minimally dependent on pressure [41].

The third vascular segment is the arteriole or the resistance vessel, which is lined with endothelium and a single layer of vascular smooth muscle. Elasticity of the arterioles, which contain very little collagen, are not pressure dependent. These are the sites of greatest hemodynamic resistance and act to control the rate of blood flow through the tissues [71]. These resistance vessels normally display a state of partial constriction, or vascular tone, making it possible to either increase or decrease the level of contractile activity to accomplish vasoconstriction or vasodilation. Whereas pulse pressure is a phenomenon of the large arteries, mean arterial pressure is a phenomenon of the small arteries and arterioles. Resistance of the arterioles (systemic vascular resistance) is calculated from the ratio of mean arterial blood pressure to cardiac output. When hypertension is present, the arterioles change, either by growth (hyperplasia or hypertrophy) or remodeling. Endothelial release of nitric oxide has relatively little effect on a large artery such as the aorta because the thick wall limits nitric oxide's effect on the media layer. However, nitric oxide released from the endothelium of the small arteries plays an important role in determining their tone and compliance [72]. Therefore, in contrast to the large arteries where compliance is largely reduced due to the rise in blood pressure, a reduction in compliance at the resistance vessel or arteriolar level may suggest endothelial dysfunction, the site of the initial injury process.

In summary, arterial compliance is a measure of the storage capacity of the arteries. Although it is recognized that the proximal aorta and its major branches are the most compliant portion of the arterial circulation, the small distal vessels contribute to the circulatory regulation. The distal vessels have a small storage capacity and are the site where the forward propagating waves are reflected back (or oscillate) centrally.

Measurement of small artery compliance may be a more sensitive marker for individuals at risk for developing the large artery abnormalities that lead to the rise in blood pressure.

2.5 Measurement of Arterial Compliance

Arterial compliance can be depicted in a pulse pressure waveform (Appendix A). The shape of the arterial pressure wave is influenced by the structure and function of the large and small arteries, and is altered as the pulse wave travels from the root of the aorta to the more distal arterial sites of measurement [73]. Ejection of blood into the aorta generates a pressure wave (incident wave) that is propagated to other arteries throughout the body. At branching points of the small arteries, waves are reflected and travel backward toward the ascending aorta. The pressure wave reflection is not a single wave but an oscillation in the system that creates a decaying wave detectable throughout diastole [55]. The amplitude and shape of the pulse pressure wave is determined by the incident wave generated by left ventricular stroke volume, the reflected waves or oscillations that originate at arterial branch points and in the microcirculation, viscosity of the blood, and the structure and tone of various segments of the arterial vasculature [74]. Typically, the systolic pressure rises steeply and then drops rapidly toward a dicrotic notch which occurs with closure of the aortic valve, followed by a small hump representing the oscillatory or reflective increase in arterial pressure (Appendix A) [75]. The typical waveform should also demonstrate a smooth and gradual decline from the dicrotic notch area toward the lowest diastolic value, known as the diastolic decay curve. As the arterial compliance decreases with disease or aging however, the vessels become stiffer and the forward waves are reflected back

earlier into the proximal arterial system to collide with the forward propagating waves. This produces increased wave amplitude and a flatter systolic peak. The dicrotic notch becomes less prominent and may even disappear entirely being superimposed onto the initial diastolic decay. The diastolic decay curve also presents a sharper decline and is no longer gradual. These alterations in reflected pulse wave augment systolic pressure, placing a greater load on the heart. This has been supported experimentally with a more compliant arterial circulation minimizing cardiac work and providing adequate coronary perfusion [76,77].

One of the non-invasive methods to assess arterial compliance is diastolic pulse wave analysis. This method is based on an electrical circuit called the modified Windkessel model [45] to represent components of the arterial vascular system. In electrical terms, where Ohm's law states that current is equal to the ratio of voltage to resistance (I=V/R), the flow rate of blood is similar to the current, the pressure gradient (difference in pressure between the beginning and end of a vessel) is similar to the voltage, and resistance of the blood vessels acts as the resistance in the equation. This flow rate is like alternating current, since blood is pumped intermittently. The pressure gradient is the main driving force for flow thorough the vessel, however when the resistance increases, the pressure gradient must concomitantly increase to maintain the same flow rate, thus increasing work of the heart. A zero order model would assume a simple linear relationship where pressure (voltage) and volume of blood flow (current) are proportional to each other and resistance remains constant. However, this representation of a human arterial system is too simplistic, and the resistance likely changes with an increase in pressure or rate of flow. The first order model (Windkessel

model) has a single capacitator element in parallel with a resistance element. This model, however, does not produce the waveforms observed during diastole. The modified model has two capacitance elements (large and small vessel compliance), inertance (inertia of the blood), and a resistance element (systemic vascular resistance) to produce a third-order model (Appendix B). Capacitators are resistor elements that have the ability to store energy and impede changes in the pulsatile pressure (voltage) through the circuit, and inductors (represented by inertance) are resistors that can impede changes in the blood flow rate (current). The principle of the model is that the arterial tree is loaded in systole by the stroke volume, and after aortic valve closure, the diastolic pressure contour is a function of resistance, compliance and inertance of an isolated arterial system. The site of measurement therefore is theoretically unimportant, because the system is closed and pressure is transmitted within the system [55]. The model is used to mathematically calculate the diastolic decay curve into a general exponential decay component (C1, capacitative compliance of the large arterial system), and an oscillatory component (C2, oscillatory or reflective compliance of the distal or smaller vessels). This is the simplest model that can produce both the general exponential decay and the decaying oscillatory pressure waveform seen during diastole in peripheral arterial sites [78]. C1 represents the ability of the large and medium-sized conduit arteries such as the aorta, femoral and radial arteries to accommodate to the change in volume and pressure of blood. C2 is more distal and primarily influences the frequency and rate of decay of the oscillatory pressure waves that originate at reflecting sites in the small arteries [78]. There is no distinct anatomical separation between large and small arteries. The sites of oscillations are largely microscopic at

branching points of the arterial tree. The dampening of the pressure oscillations that result from intermittent ventricular ejection is known as the "Windkessel effect" [79]. Each circuit element in the third order model does not represent a single vascular property, but rather each element contributes to the pressure waveform that is observed in real subjects [78]. Due to the nonlinear pressure-volume relationship of the large arteries, C1 is sensitive to increases in blood pressure. In contrast, C2 appears to be independent of pressure. An increase in speed and amplitude of the reflective waves at branching points (decrease in C2) may be more attributable to an effect directly on the structure or function of the small artery walls [47]. This has been supported experimentally with a study showing that when hypertensive patients were compared with age-matched normal controls, C1 was lower and C2 was strikingly lower in the hypertensives [80], and intravenous infusion of the nitric oxide synthase inhibitor (L-NAME) into healthy subjects reduces C2 and increases blood pressure without affecting C1 [81]. This suggests that a reduction in C2 may reflect endothelial dysfunction. More importantly, McVeigh et al demonstrated that selective alteration in the distal vasculature occurs even in the absence of hypertension [7]. C2 has been identified as a more sensitive marker of structural and functional abnormalities associated with diabetes [7], smoking [82], atherosclerosis [47,83], heart failure [84], target organ damage [85] and cardiovascular events [6] in adults.

Large and small artery compliance can be measured with a non-invasive device using applanation tonometry of the radial artery (HDI/PulseWave CR-2000, Hypertension Diagnostics, Inc., Eagan MN). The applanation method is a measurement of the force required to flatten a certain area [46]. A tonometer is a calibrated device

that is strapped to the wrist with a pressure transducer placed over the radial artery. A blood pressure cuff is placed on the opposite arm. The transducer uses a piezoelectric crystal to convert the mechanical movement of the blood vessel into electrical energy and determine the elasticity. Measurement of C1 and C2 are based on estimates of stroke volume, ejection time and cardiac output that are calculated from an algorithm that uses height, weight, blood pressure, and heart rate.

Although there is presently no gold standard for measurement of arterial compliance, diastolic pressure waveforms of pulse contour analysis have been validated in adults against brachial intra-arterial waveforms ($r = 0.82$ for C1, $p<.001$ and $r = 0.62$ for C2, $p<.001$) [47]. The PulseWave CR-2000 has been shown to be reproducible over both a 15-minute time course ($r = 0.73$ for C1 and 0.84 for C2) and 3-week time course ($r = 0.59$, $p<0.05$ for C1 and $r = 0.73$, $p<0.05$ for C2) [10].

Damage to the endothelium, whether caused by hypertension, diabetes, elevated cholesterol, smoking, physical inactivity, aging, or combinations of these risk factors, appears to be key in the progression of atherosclerosis and cardiovascular events. As such, endothelial dysfunction and arterial compliance have recently been identified as novel risk markers for CVD. Cardiovascular events result from vascular accidents occurring in arteries with already-present abnormal structure and function. Because endothelial function is directly involved in maintaining normal arterial tone and preventing vascular smooth muscle hypertrophy, maintenance of a normal arterial compliance depends on sufficient nitric oxide release and its effect on vasodilation. Hypertension is often associated with elevated levels of angiotensin-II, leading to reduced vasodilation. Therefore, the relationship between endothelial function and

arterial compliance is clearly important. Arterial compliance has been shown to significantly correlate with endothelial function [86,87], and it has been suggested that the measurement of arterial compliance may serve as a surrogate marker [55]. Like impaired endothelial function, decreased arterial compliance is associated with the major risk factors for CVD such as diabetes mellitus [7], obesity [11], hypercholesterolemia [12], smoking [8], physical inactivity [9] and advancing age [10]. The remainder of this review will focus on physical inactivity as a risk factor for CVD and its effect on vascular function.

2.6 Impact of Physical Inactivity on Arterial Compliance

In 2001, the World Health Organization reported that 1.9 million global deaths were attributed directly to physical inactivity. Specifically, physical inactivity caused 15% of some cancers, diabetes and heart disease [88].

The first studies to assess the relationship between physical activity and the development of CVD were conducted by Morris et al [89,90] who compared the mortality rate between male postmen who delivered mail to their sedentary telephone clerks in the postal office. Deaths among the telephone clerks were more than two times higher than the postmen. Physical inactivity and low levels of fitness are associated with obesity and hypertension in children, adolescents and adults [29,30]. In adults, both physical inactivity and decreased aerobic fitness are strongly associated with the development of CVD and all-cause mortality [91-93]. Even leisure time physical activity is inversely associated with all-cause mortality [94]. Additionally, prospective studies in adults have shown that lower fitness levels are associated with a higher risk of stroke [95], hypertension [96], type II diabetes [97], osteoporotic fractures

[98], depression [99] elevated C-reactive protein [100] and some cancers [101]. Since clinical events are extremely rare in children, the ability of physical activity in childhood to predict exercise habits in adulthood and its impact on classic and novel CVD risk markers is of utmost importance.

In the Framingham Children's Study [102] inactive preschoolers were nearly four times as likely to have a greater amount of subcutaneous fat compared to active preschoolers. Also, increased blood pressure and poor lipid profiles were associated with low levels of physical activity. Twisk et al [103] have shown that the most important lifestyle parameter discriminating participants at high risk from those at low risk for developing CVD was daily physical activity. This lifestyle parameter was found to be positively related to peak aerobic power (VO_{2peak}) and inversely related to percent body fat. In adults, nitric oxide concentrations are positively correlated with VO_{2peak} [104]. Although essential hypertension in childhood rarely causes serious morbidity, Litwin et al [105] showed that in newly diagnosed children with hypertension, increases in carotid and femoral intima media thickness occur. In addition, physical activity has been shown to positively influence endothelial function in children and adolescents aged 5 to 14 years [106,107], and arterial compliance (as measured by diastolic pulse wave analysis) in children aged 9 to 12 years [108]. While in children and adolescents there is a direct relationship between the number of risk factors present and severity of atherosclerosis (i.e. number of fatty streaks) [48,109], the relationship between physical activity, aerobic fitness and CVD risk in children is less well established than in adults.

Physical activity levels in children peak in the early teenage years and then dramatically decline thereafter [110-113]. Based on the results of the 2002 Physical Activity Monitor [16], a national survey of Canadians' physical activity patterns, 56% of Canadian adolescents between 12 and 19 years of age are not physically active enough to achieve desired health benefits. Furthermore, over half of Canadian teenagers are sedentary, with only 18% performing enough daily activity to meet the International Guidelines for optimal growth and development. The International Guidelines for Physical Activity, established in 1994, recommended that all adolescents be physically active each day, and engage in at least 20 minutes of vigorous physical activity at least 3 days per week [16]. More recently, the American College of Sports Medicine recommends the same physical activity guidelines for adolescents as that of adults: each individual should engage in 30 minutes of moderate intensity physical activity on most if not all days of the week [42].

It is well established that physical activity patterns and fitness tend to track from childhood into adulthood [20,22,114,115]. There is also an additive impact of risk factors for CVD when they exist together [116]. An increasing number of epidemiologic studies have documented the prevalence of three or more risk factors in children and adolescents [14,117-121]. With the accumulating documentation of unfavorable blood pressure, insulin sensitivity levels and lipid profiles in young children with low levels of physical activity, childhood and adolescence appear to be the critical times to promote good exercise habits and to prevent sedentary behavior in adulthood. School- and community-based intervention programs can help attenuate the tendency towards inactivity with increasing age. Support for this comes from

implementation of standardized physical education classes which have increased children's and adolescent's physical activity levels in four communities [122]. Promotion of active lifestyle and education regarding physical fitness has been shown to be very effective in modifying risk factors [110,113,123].

2.7 Decline in Aerobic Capacity over the Lifespan

There is an age-mediated decline in aerobic capacity by approximately 10% per decade beginning in the second decade of life [124]. Since the age-mediated decline in aerobic capacity is associated with an increased risk of cardiovascular and all-cause mortality and disability [125], it is important to maintain aerobic fitness as individuals age to preserve physiological functioning capacity.

Age and gender-associated differences in aerobic capacity during growth are well documented [126,127]. In males, aerobic capacity remains relatively stable throughout childhood and adolescence while in females it remains fairly stable until about 12 years of age and then begins to decline through adolescence [128]. In addition to the decline in aerobic capacity in adolescent females, there has been an estimated additional decline of about 20% over the past few decades in 15 to 18 year old American females [129]. A strong positive correlation between arterial compliance and aerobic capacity exists in healthy younger and older adults [130,131].

2.8 Effects of Exercise on Vascular Function

It has been suggested that arterial compliance may be a better predictor of "biological age" than chronological age [2], implying that the cardiovascular system of an elderly athlete may be biologically younger than that of a sedentary individual of the same age. A number of cross-sectional studies provide support for the role that regular

aerobic exercise may play in attenuating the age-mediated decline in arterial compliance. Findings from the Baltimore Longitudinal Study on Aging reveal that masters athletes (≥ 30 years) demonstrated lower aortic pulse wave velocity and carotid augmentation index (other indices of arterial compliance) compared to age-matched healthy controls [37]. Also, aerobic capacity was positively associated with arterial compliance and was the strongest independent predictor of aortic pulse wave velocity and augmentation index. In a follow-up study on healthy men, carotid artery compliance declined significantly with age regardless of habitual exercise, however the age-associated difference was only about half as great in endurance exercise-trained compared with sedentary subjects [9]. In addition, men who were recreationally active only had small declines in carotid compliance compared with age than the sedentary men. Recent studies in endurance-trained male athletes demonstrated that endothelium-dependent vasodilation is higher than sedentary age-matched controls [104,132], and is preserved with aging, whereas it declines markedly with aging in sedentary healthy men aged 22-72 years [104]. Decreases in large artery compliance with age in sedentary women are also associated with increases in 24-hour systolic blood pressure and arterial pulse pressure, however, these findings were absent in endurance-trained women [133]. These results suggest that regular aerobic exercise might slow or prevent increases in arterial stiffness as well as the age-associated elevations in blood pressure.

Exercise can also reverse arterial stiffening. Programs of moderate intensity aerobic exercise ranging from one to three months in duration have been shown to increase endothelial function [134,135], carotid artery compliance [9], femoral intima-

media thickness [136], and aortic pulse wave velocity [137,138] in previously sedentary young (18 years) and older (80 years) individuals. Tanaka et al [139] found that the improvement in carotid arterial compliance was not associated with changes in body weight, adiposity, blood pressure, plasma cholesterol, or resting heart rate, indicating a direct effect of exercise on arterial compliance. Importantly, this was accomplished with a type of physical activity (walking) that can be performed by most, if not all healthy individuals. Exercise training programs have even been shown to improve arterial compliance and endothelial function in individuals with established coronary artery disease [140,141], essential hypertension [142], and congestive heart failure [143,144]. Recent reports have also demonstrated the positive effects of exercise training on endothelial function in obese children and adolescents [145-147]. Taken together, the findings of these studies show that reductions in vascular function are reversible, and can be favorably affected by exercise.

It has been suggested that physical activity could favorably influence arterial stiffness independently of cardiorespiratory fitness [139,148]. However, Boreham et al [149] recently demonstrated that the increased arterial compliance associated with physically active individuals was only seen in those who performed activities or sports that also increased cardiorespiratory fitness. They concluded that physical activity may need to be cardiovascular in nature and a type leading to improvements in cardiopulmonary fitness levels for an increase in arterial compliance to be seen. The authors also found work- or leisure-time-related activities were not associated with increased arterial compliance. This too contrasts previous studies [38,39]. Conversely, it has also been suggested that associations, or lack thereof, between physical activity or

leisure-time and work activities and measures of arterial compliance are likely to be much less reliable than measures of cardiorespiratory fitness [150]. Measures of physical activity and leisure-time activities are often based on questionnaires, which are subjective and may be confounded by under- or over-reporting. This limitation may be the reason for the discrepancy in the literature.

2.9 Gender Differences in Physical Fitness

Understanding the influence of gender on vascular function has relevance in determining if males or females are at greater risk for developing arterial stiffness, especially if one group has a higher incidence of cardiovascular risk factors such as decreased fitness. Whereas the aerobic capacity of boys and girls are similar in 6-7 year olds, there is ample evidence of differentiation thereafter. Both cross-sectional and longitudinal studies have shown that boys' cardiorespiratory fitness is fairly consistent over the age of 8 to 16 while girls demonstrate a decrease in peak aerobic power (VO_{2peak}) [126,151]. The available data shows that boys' VO_{2peak} become significantly greater compared to girls by the age of 10 years [152], and this has been attributed at least in part to their greater muscle mass and hemoglobin concentration [126] and lower levels of subcutaneous fat [151].

Consistent evidence shows that there are gender differences in levels of participation in physical activity, with boys being more fit and physically active and less fat than girls in both childhood and adolescence [17,25,26,153,154]. It is hypothesized that explanations for these sex differences are in economic, environmental and social variables such as parental and cultural beliefs regarding which activities are appropriate for girls [153].

Clearly, the effect of gender on arterial compliance is important if adolescent females have reduced compliance compared to males, as this would put them at greater risk with lower physical activity and fitness levels.

2.10 Influence of Gender on Vascular Function

Data regarding the influence of gender on vascular function in adults has been inconsistent. Some studies have demonstrated that women have reduced arterial compliance compared to men, with a greater age-mediated decline [155-168]. Of these studies, some have attributed such differences to differences in body height and size [10,160,161,165-167]. An inverse relationship between body height and the risk of CVD has been observed and persists even after adjustment of known heart disease risk factors [169]. Some studies measuring arterial compliance in individuals from birth into adulthood reveal an increase in arterial compliance in both males and females until adolescence at which point it peaks, and then steadily decreases with increasing age [160,165], suggesting a strong influence of body height. Reflected waves are thought to be more prominent in women because smaller arteries and a shorter arterial tree will cause amplification of pressure and velocity pulse wave, increased aortic tapering and induce a faster heart rate which increases cardiac work and shortens diastole [170]. In a study of 85 men, multiple regression analysis showed that body height and aortic pulse wave velocity were the principal determinants of travel time and height of the reflected wave, short stature being associated with a short travel time and increased reflections [171]. Despite this evidence, decreased arterial compliance has been reported in women even after adjustment for height and size [158,159,163].

In contrast, several studies have also found that women have either similar or better vascular function compared to men [12,37,166,172-182], but that after menopause arterial compliance and endothelial function is decreased in women [162,172,181,183]. One previous study looked at vascular function pre- and post puberty [184]. The authors found higher pulse wave velocity (decreased compliance) in females pre-puberty, but no differences post-puberty. This suggests that both intrinsic and hormonal influences may contribute to arterial compliance.

In studies using diastolic pulse wave analysis, gender differences in C1 and C2 have been reported but only beginning in young adulthood. Two studies [10,185] found women had greater age-mediated decline in C1 and C2 than men in individuals aged 21 to 80 years. Winer et al [163] also noted lower arterial compliance in younger women (age 24 years) compared to men, but this was only significant for C2. Conversely, three studies failed to show differences in C1 or C1 between genders in subjects aged 23 [177], 12 years of age [186], and between ages 9 to 12 [108].

In summary, despite the marked differences in prevalence of atherosclerotic disease, data regarding gender-related differences in large and small artery mechanical properties remain contradictory and inconclusive. Whether females indeed have reduced arterial compliance compared to males due to shorter stature and smaller vessels, or similar or even increased arterial compliance due to estrogen hormones is unclear. The confusion in this area calls into question the difference in methods used for measuring arterial stiffness, as well as the methods in which confounding variables such as hormone replacement therapy, height, body mass, blood pressure etc. have been accounted for. The vast majority of the literature suggests that there is a gender

difference, with women prone to having decreased arterial compliance compared to men during times when estrogen levels are at their lowest i.e. pre-puberty and post-menopause, and may have a greater age-mediated decline due to shorter stature or smaller arteries. Conceivably, a gender difference in vascular function does not exist until after a certain age when the differences in height and hormone levels become more apparent between boys and girls.

2.11 Summary

In summary, the impact of physical activity and gender on vascular function in children and adolescents is an important research question for four reasons. First, CVD is the leading cause of death in North America and other developed countries, and both physical inactivity and low levels of physical fitness are independently related to CVD mortality in adults. Second, although the clinical manifestations of CVD occur in adulthood, studies have shown that atherosclerosis has its origins in childhood. Third, Canadian children and adolescents are adhering to a more sedentary lifestyle, females more so than males. Finally, there is also evidence that physical activity, physical fitness and CVD risk factors track from childhood and adolescence into adulthood. Thus, perhaps adult CVD can be predicted to some degree from childhood and adolescent novel risk markers such as arterial compliance, and youth at risk for adult heart disease can be targeted for intervention and education strategies.

CHAPTER 3

METHODS

3.1 Subjects and Inclusion Criteria

This study represents secondary analysis of a larger investigation that examined the impact of body mass on insulin sensitivity and arterial compliance in individuals between 5 and 19 years of age from the Black Gold School District. This study examined data from participants between 13 and 17 years of age. The rationale for choosing this age group is the observed decline in physical activity that occurs after 13 years of age [17]. Participants were grouped into four fitness quartiles according to their shuttle run scores. Based on the findings of Reed et al. [108], we expected a 1.25 mL/mmHg x 10 change in small arterial compliance between groups. The authors did not provide a standard deviation (SD), however, if the SD is 2.3 mL/mmHg x 10 with a two-tailed significance level of alpha = 0.05 and a power of 0.8, then 54 participants per fitness quartile are needed to detect differences between groups (Appendix C).

3.2 Exclusion Criteria

Students were excluded if they had any condition that prohibited a fitness assessment (i.e. severe asthma, musculoskeletal disorders), self-reported presence of diabetes or hypertension, and/or the use of medications to control blood pressure, glucose or lipid metabolism.

3.3 Study Design

This was an observational cross-sectional study that allowed for the assessment of the relationship between physical fitness and arterial compliance, and to identify if any gender differences for arterial compliance exist.

After informed consent was obtained, the participants performed a series of tests to assess their physical fitness and vascular function on two separate days. The time interval between fitness and vascular function tests ranged from one day to one week apart.

3.4 Measurement of Height and Weight

Participants' weight was measured on a calibrated digital scale while their height was measured with a plastic measuring tape placed against a wall.

3.5 Assessment of Physical Fitness

Physical fitness was assessed using a maximal exercise test called the modified Léger shuttle run [187]. The test was performed in the school gymnasium and involved running back and forth between two cones placed 20m apart. Approximately ten students ran the test at one time. A pre-recorded metronome in CD format determined the running pace and stages. Specifically, the initial pace was set at 8.0 km/h, allotting a time of 9s to complete 20m, which was attainable for all of the participants. The pace increased to 9.0 km/h after 60 seconds, and then by 0.5 km/h every minute thereafter. The test was finished when the participant was no longer able to maintain the pace or reach within approximately 3m of the cone on two consecutive laps. A half stage was attained if the participant completed at least 30 seconds of the final stage and the last stage completed was recorded as the final score. The participants exerted maximal

effort prior to stopping the test. A table of the shuttle run stages and corresponding speed and time interval between laps is presented in Appendix D.

3.6 Assessment of Arterial Compliance

Assessment of blood pressure and arterial compliance was performed with a commercially available cardiovascular profiling system (HDI/PulseWave CR-2000, Hypertension Diagnostics, Inc., Eagan MN). This non-invasive system has been used to measure blood pressure and arterial compliance in individuals between 9 and 83 years of age [10,108,186]. As part of this test, the participants were in the supine position, with their arm supported and extended at shoulder level. A blood pressure cuff was positioned on the left upper arm and the tonometer was placed on the right hand with the pressure transducer placed over the radial artery (Figure 1).

Figure 1. Cardiovascular Profiling System

Placement and pressure adjustment of the transducer was continued until a visually acceptable waveform was achieved on the monitor. Analysis of the diastolic

portion of the pulse wave was performed on a 30-second recording of the radial artery pressure waveforms. Systolic and diastolic blood pressure, heart rate, systemic vascular resistance, total vascular impedance, cardiac output, cardiac index, C1 and C2 were then recorded from the monitor for two consecutive recordings.

3.7 Statistical Analysis

Data are reported as mean ± standard deviations for age, height, weight, body mass index, systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP), cardiac output, cardiac index, heart rate, total vascular impedance, stroke volume, systemic vascular resistance, and Legér shuttle run score. All continuous variables, except for shuttle run score, are reported as the average of two consecutive recordings. Nominal data, including smoking status and gender, are reported as a percentage. Analysis of variance (ANOVA) was used to determine if differences in the measured variables were found between fitness quartiles and gender. Post hoc analysis was performed with Tukeys' HSD test. Mann-Whitney U tests were used for ordinal data while chi-squared tests were performed to detect differences in categorical variables. If differences existed, an analysis of covariance (ANCOVA) was used to adjust for statistically significant variables, otherwise an ANOVA was used. The same method was applied in the secondary analysis to determine the impact of gender on arterial compliance. Predictors of arterial compliance were determined by stepwise multiple linear regression. Normal distribution of data was checked against scatter plots. The alpha level was set "α prori" at $p<0.05$.

3.8 Outcome Measures

The primary outcome measures were C1 and C2. The independent variable for the primary outcome was physical fitness (Legér shuttle run score) and gender for the secondary outcome measure. A sample data collection sheet is shown in Appendix E.

3.9 Ethical Considerations

Ethical approval for the primary study as well as approval to conduct secondary analysis was obtained from the University of Alberta Health Research Ethics Board (Appendix F).

CHAPTER 4

RESULTS

4.1 Descriptive Data

The study included 247 participants between 13 and 17 years of age (mean age 14 ± 1 years, Table 1). There were 112 males and 135 females. The participants' resting systolic blood pressure was 118 ± 10 mmHg and resting diastolic blood pressure was 62 ± 7 mmHg. The average height was 166 ± 10 cm, while the mean body mass index was 21 ± 4 Kg/m^2. Shuttle run scores ranged from 1.0 (lowest attainable score) to 14.0, with a mean score of 7.1 ± 3.0. The participants' resting heart rate was 74 ± 14 beats per minute while the stroke volume and cardiac index were 77 ± 18 and 3.3 ± 0.4 $L/min/m^2$, respectively. Systemic vascular resistance was 1249 ± 379 ($dynes/sec/cm^5$), while the total vascular impedance was 136 ± 42 $dynes/sec/cm^5$. Finally, the participants' C1 and C2 were 13.7 ± 4.4 ml/mmHg x 10 and 8.0 ± 2.5 ml/mmHg x 100, respectively (Table 1). Scatter plots of all measured variables demonstrated normality of data.

4.2 Physical Fitness and Arterial Compliance

There were 79, 59, 53 and 56 participants in the first to fourth fitness quartiles (Table 2). There were fewer females in quartiles 3 and 4 compared to quartiles 1 and 2. Individuals were significantly taller in quartile 3 versus quartile 1 and 2, while body mass index was significantly higher in the lowest fit group compared to the other groups. A significant difference was found between the fitness quartiles. Specifically, the participants in quartile 1 were 40% to 66% less fit than the other three groups ($p<0.0001$). Large and small arterial compliance were not significantly different

between the four fitness quartiles. Finally, no significant differences were found for any other variable between groups.

4.3 Effect of Gender on Physical Fitness and Arterial Compliance

Males were taller (Males: 170 ± 10 cm vs. Females: 163 ± 8 cm, $p<0.0001$), heavier (Males: 63 ± 16 Kg vs. Females: 57 ± 12 Kg, $p=0.004$), and had a higher shuttle run score (Males: 8.2 ± 3.1 vs. Females: 6.2 ± 2.5 and, $p<0.0001$) compared to females. Both systolic and diastolic blood pressure were different between genders, with males having higher systolic blood pressure (Males: 121 ± 11 mmHg vs. Females: 116 ± 10 mmHg, $p=0.001$) but lower diastolic blood pressure (Males: 61 ± 7 mmHg vs. Females: 63 ± 7 mmHg, $p=0.03$). Resting stroke volume (Males: 80 ± 19 mL vs. Females: 75 ± 18 mL, $p=0.04$) and cardiac output (Males: 5.7 ± 1.1 L/min vs. Females: 5.4 ± 0.8 L/min, $p=0.03$) were higher in males compared to females. Small arterial compliance was significantly higher in males than in females, however, after controlling for differences in height, weight, systolic blood pressure, diastolic blood pressure, stroke volume, shuttle run score and cardiac output, the difference no longer existed. No other outcomes measured were significantly different between the groups.

4.4 Predictors of Arterial Compliance

The results of the linear stepwise regression analyses are presented in Tables 4 and 5. The variables used to predict arterial compliance were: gender, shuttle run score, height, weight, systolic and diastolic blood pressure, heart rate, systemic vascular resistance and stroke volume. Because large artery compliance is highly correlated to blood pressure, and small artery compliance is greatly dependent on systemic vascular resistance, a second regression analysis was conducted as a sensitivity analysis, where

systolic and diastolic blood pressure and systemic vascular resistance were omitted from the regression analysis. In the first analysis, the independent predictors of C1 were systolic and diastolic blood pressure, weight, stroke volume and shuttle run score. These predictors account for 40% of the total variance observed. Systolic blood pressure was the strongest predictor, having a negative effect on large artery compliance. Small artery compliance was predicted by weight, systemic vascular resistance, systolic blood pressure and shuttle run score, and accounted for 32% of the total variance explained. The strongest predictor of C2 was weight, having a positive effect. In the second analysis, large artery compliance was positively predicted by stroke volume and weight, the strongest predictor being stroke volume with a positive effect. This model accounted for 24% of the total variance observed. Small artery compliance was predicted by weight, shuttle run score and height, and this model accounted for 20% of the total variance observed. Weight was the strongest predictor of C2 in the second analysis, again having a positive effect. Validity of both models is supported by Cook's Distance and dbBeta tests which revealed no values greater than 1.0.

Table 1. Subject Characteristics

Variable	Mean (n = 247)
Gender	135 Female (55%)
	112 Male (45%)
Age (y)	14 ± 1
Height (cm)	166 ± 10
Weight (kg)	60 ± 14
Body mass index (kg/m^2)	21 ± 4
Shuttle run score (stage)	7.1 ± 3.0
Systolic blood pressure (mmHg)	118 ± 10
Diastolic blood pressure (mmHg)	62 ± 7
Mean arterial pressure (mmHg)	83 ± 8
Heart rate (beats per minute)	74 ± 14
Systemic vascular resistance ($dynes/sec/cm^5$)	1249 ± 379
Total vascular impedance ($dynes/sec/cm^5$)	136 ± 42
Large arterial compliance (mL/mmHg x 10)	13.7 ± 4.4
Small arterial compliance (mL/mmHg x 100)	8.0 ± 2.5
Stroke volume (mL)	77 ± 18
Cardiac output (L/min)	5.5 ± 1.0
Cardiac index ($L/min/m^2$)	3.3 ± 0.4
Current smokers	7 (3.2%)

(values are mean ± SD)

Table 2. Physical Fitness and Arterial Compliance

	Quartile 1 1.0-5.0	Quartile 2 5.5-7.0	Quartile 3 7.5-9.5	Quartile 4 10.0-14.0	P
n (247)	79 (32%)	59 (24%)	53 (21%)	56 (24%)	-
Shuttle run score (stage)	3.8 ± 1.0 +‡▲	6.4 ± 0.6 *‡▲	8.3 ± 0.7 *+▲	11.3 ± 1.2 *+‡	<0.0001
Gender	60F (76%) 19M (24%)	36F (61%) 23M (39%)	22F (42%) 31M (59%) *+	17F (30%) 39M (70%)*+	<0.0001
Current smokers	3 (5%)	1 (2%)	1 (2%)	2 (4%)	0.8
Age (y)	14 ± 1	14 ± 1	15 ± 1	14 ± 1	0.2
Height (cm)	164 ± 8	165 ± 10	170 ± 10 *+	168 ± 10	0.001
Weight (kg)	62 ± 16	58 ± 12	60 ± 13	58 ± 11	0.3
Body mass index (kg/m^2)	23 ± 5 +‡▲	21 ± 3	21 ± 3	21 ± 3	0.001
Systolic Blood Pressure (mmHg)	118 ± 9	118 ± 10	117 ± 12	120 ± 11	0.7
Diastolic Blood Pressure (mmHg)	63 ± 6	63 ± 8	60 ± 7	61 ± 7	0.1
Mean Arterial Pressure (mmHg)	83 ± 7	84 ± 8	81 ± 8	83 ± 9	0.5
Heart rate (bpm)	76 ± 13	77 ± 15	71 ± 13	72 ± 14	0.02
Systemic Vascular Resistance ($dynes/sec/cm^5$)	1233 ± 294	1291 ± 371	1176 ± 241	1294 ± 558	0.3
Total Vascular Impedance ($dynes/sec/cm^5$)	135 ± 47	140 ± 42	133 ± 38	135 ± 37	0.9
Stroke volume (mL)	76 ± 18	74 ± 18	81 ± 17	78 ± 20	0.1
Cardiac output (L/min)	5.6 ± 1.0	5.4 ± 0.9	5.6 ± 0.8	5.4 ± 1.0	0.5
Cardiac index ($L/min/m^2$)	3.4 ± 0.3	3.3 ± 0.4	3.3 ± 0.3	3.2 ± 0.5	0.2
Large Artery Complaince (C1) (mL/mmHg x 10)	13.9 ± 5.3	12.5 ± 3.3	14.1 ± 3.5	14.2 ± 4.7	0.1
Small Artery Compliance (C2) (mL/mmHg x 10)	7.6 ± 2.7	7.5 ± 2.1	8.4 ± 2.2	8.4 ± 2.7	0.08

(*, $p < 0.05$ vs. Quartile 1 ; +, $p < 0.05$ vs. Quartile 2 ; ‡, $p < 0.05$ vs. Quartile 3 ; ▲, $p < 0.05$ vs. Quartile 4, values are mean ± SD)

Table 3. Effect of Gender on Physical Fitness and Arterial Compliance

Variable	Females	Males	P
n (247)	135 (55%)	112 (45%)	-
Age (y)	14 ± 1	14 ± 1	0.5
Height (cm)	163 ± 8	170 ± 10	<0.0001
Weight (kg)	57 ± 12	63 ± 16	0.004
Body mass index (Kg/m^2)	22 ± 4	21 ± 4	0.7
Shuttle run score (stage)	6.2 ± 2.5	8.2 ± 3.1	<0.0001
Heart rate (beats per minute)	75 ± 13	73 ± 14	0.5
Systolic blood pressure (mmHg)	116 ± 10	121 ± 11	0.001
Diastolic blood pressure (mmHg)	63 ± 7	61 ± 7	0.03
Mean arterial pressure (mmHg)	82 ± 7	83 ± 8	0.4
Systemic vascular resistance ($dynes/sec/cm^5$)	1264 ± 319	1229 ± 442	0.5
Total vascular impedance ($dynes/sec/cm^5$)	134 ± 40	138 ± 44	0.4
Stroke volume (mL)	75 ± 18	80 ± 19	0.04
Cardiac output (L/min)	5.4 ± 0.8	5.7 ± 1.1	0.03
Cardiac index ($L/min/m^2$)	3.3 ± 0.3	3.3 ± 0.4	0.1
Current smokers	6 (4%)	1 (1%)	0.1
Large artery compliance (mL/mmHg x 10)	13.7 ± 4.1	13.7 ± 4.7	1.0
Small artery compliance (mL/mmHg x 100)	7.5 ± 2.1	8.4 ± 2.8	0.003

(values are mean ± SD)

Table 4. Predictors of Large and Small Arterial Compliance

Large Artery Compliance (C1)	**p**	**Standardized Beta Coefficient**
Systolic Blood Pressure	<0.0001	-0.582
Weight	<0.0001	0.480
Diastolic Blood Pressure	<0.0001	0.295
Stroke Volume	<0.0001	0.281
Shuttle Run Score	0.02	0.126
(Using Cooks Distance and dbBeta tests, no values were >1.0)		
Small Artery Compliance (C2)	**p**	**Standardized Beta Coefficient**
Weight	<0.0001	0.433
Systemic Vascular Resistance	<0.0001	-0.236
Systolic Blood Pressure	<0.0001	-0.257
Shuttle Run Score	<0.0001	0.227
(Using Cooks Distance and dbBeta tests, no values were >1.0)		

Large Artery Model: $r = 0.64$, adjusted $r^2 = 0.40$, $p < 0.0001$
Small Artery Model: $r = 0.58$, adjusted $r^2 = 0.32$, $p < 0.0001$

Table 5. Sensitivity Analysis for Predictors of Large and Small Artery Compliance

Large Artery Compliance (C1)	**p**	**Standardized Beta Coefficient**
Stroke Volume	<0.0001	0.307
Weight	<0.0001	0.247
(Using Cooks Distance and dbBeta tests, no values were >1.0)		
Small Artery Compliance (C2)	**p**	**Standardized Beta Coefficient**
Weight	<0.0001	0.301
Shuttle Run Score	0.006	0.171
Height	0.04	0.167
(Using Cooks Distance and dbBeta tests, no values were >1.0)		

Large Artery Model: $r = 0.49$, adjusted $r^2 = 0.24$, $p < 0.0001$
Small Artery Model: $r = 0.46$, adjusted $r^2 = 0.20$, $p < 0.0001$

CHAPTER 5

DISCUSSION

5.1 Main Findings

The main finding of this investigation was that there is no significant difference for large or small artery compliance between adolescents with the highest shuttle run score compared to adolescents with the lowest shuttle run score (physically fit and unfit individuals) between 13 and 17 years of age. In addition, no significant difference was found between males and females for large or small artery compliance. Large artery compliance was predicted by weight, shuttle run score, systolic and diastolic blood pressure and stroke volume. Finally, small artery compliance was predicted by systemic vascular resistance, weight, systolic blood pressure and shuttle run score.

5.2 Effect of Physical Fitness on Arterial Compliance

Currently, there is a paucity of studies that have examined the effect of physical fitness on arterial compliance in younger individuals. Treiber et al [107] found that enhanced cardiorespiratory fitness was associated with greater vascular function in individuals between 11 and 14 years of age. Specifically, adolescents who had the highest cardiovascular fitness (i.e., lower heart rate response during submaximal exercise) also had the most favorable femoral artery endothelial function. Consistent with our findings, Abbot et al [106] reported that younger individuals (age 6 to 11 years) in the highest physical activity tertile (calculated as the ratio of total energy expenditure to resting metabolic rate) had greater vascular function (brachial artery flow-mediated dilation) compared to children in the lowest physical activity tertile. Reed et al [108] also showed a significant difference in small artery compliance

between the first and fourth fitness quartiles (assessed by Legér shuttle run) in children aged 9 to 12 years. A series of intervention studies have extended these findings by demonstrating a benefit of exercise training on vascular function. Exercise training programs have been shown to significantly improve brachial artery flow-mediated dilation in obese children and adolescents between 9 and 14 years of age [145-147,188]. A limitation of these studies, however, was that physical activity was measured using indirect techniques. Moreover, measures of physical fitness were performed using submaximal exercise tests, which are not true representations of maximal fitness levels. Conversely, the Legér shuttle run used in the present study is a direct measure of peak physical fitness, known to adequately predict aerobic capacity in adolescents [189].

Our finding of no significant difference in large or small arterial compliance between fitness quartiles is different than previous studies. This may be due to a difference in measurement techniques. All but one of the previous studies measured vascular function with brachial or femoral artery flow-mediated dilation. Although arterial compliance has been suggested to be a surrogate marker for endothelial flow-mediated dilation, it is possible that diastolic pulse wave analysis is not sensitive enough to detect differences in arterial compliance caused by physical fitness in adolescents, whose vascular system is not fully mature. In addition, the present study may have been underpowered to detect significant differences due to an underestimation of the standard deviation used for sample size calculation. However, although not statistically different, the lowest fit group had a 10% lower C2 than the highest fit group. Regardless of the statistical difference, our finding that the highest fit group had the best small artery compliance is consistent with Abbot et al [106] and Reed et al

[108]. Furthermore, linear regression analysis showed that shuttle run score was an independent predictor of both large and small arterial compliance, which is also consistent with previous studies. This observation remained true for small artery compliance when systolic and diastolic blood pressure and systemic vascular resistance were removed from the second regression analysis.

The mechanism for the beneficial effect of physical fitness on arterial compliance is not well known, however, a likely explanation is the enhanced blood flow through the vessel lumen during exercise that leads to acute increases in vascular shear stress. This stimulates the endothelium to release nitric oxide and concomitant vasodilation to normalize the shear stress [190]. Repeated exposure to increased shear stress as a result of exercise training may produce chronically raised levels of nitric oxide production, mediated by an increase in the expression of the nitric oxide synthase gene, and/or decreased degradation of nitric oxide by oxidative stress, and thus improve endothelial and overall vascular function. Exercise training has been shown to augment nitric oxide availability [191,192] and, in many studies, improve endothelial-dependent vasodilation [193].

The important role that cardiorespiratory fitness can play on the etiology of arterial stiffness related-diseases such as left-ventricular hypertrophy, heart failure and stroke in adults is well known. If physical fitness can affect vascular function as early as 13 years of age, the importance of fitness to prevent disease must be emphasized early in childhood and adolescence so that healthy lifestyle choices are carried on into adulthood and throughout the lifespan.

5.3 Effect of Gender on Arterial Compliance

Our study failed to show a gender difference in large artery compliance. There was, however, a significant difference in small artery compliance between genders before adjustment of anthropometric and hemodynamic differences. These results suggest that the gender difference observed is likely due to differences in intrinsic characteristics such as height and weight (vessel length and diameter), physical fitness, stroke volume, blood pressure and cardiac output. Many of these physical differences could be due to growth-associated pubertal changes. Height only emerged as an independent predictor of C2 when systolic and diastolic blood pressure and systemic vascular resistance were removed from the second regression analysis, which differs from two previous studies that found height to be a positive predictor of only C1 in children (9 to 12 years) [108] and positive predictor of both C1 and C2 in young adults (23 years) [177]. The reason for the difference in impact of height on large versus small artery compliance is not clear, however, could be due to age and/or the influence of pubertal status. Generally, these results suggest that a shorter stature and smaller body size (as often the case in females) can decrease arterial compliance. Our finding of a lack difference in either C1 or C2 between males and females is similar to previous studies using diastolic pulse wave analysis in children (9 to 12 years) [108,186] and young adults (23 years) [177]. In addition, Ahimastos et al [184] found females to have reduced large artery compliance (measured by pulse wave velocity) compared to males pre-puberty, and no difference in large artery compliance post puberty. The post-puberty group had a mean age of 15.9 years and was quite similar to the participants in the present study. Post-pubertal males were taller and

heavier, had greater cardiac output, higher systolic blood pressure and lower diastolic pressure compared to post-pubertal females, however, no differences in arterial compliance were observed. It is possible that the majority of the females in our sample had developed estrogen levels sufficient enough to offset an unfavorable influence of shorter stature, and hence explain why no gender difference in C1 and C2 was observed.

The findings from previous studies suggest that gender differences in arterial compliance are, in part, due to the influence of sex hormones, because these differences tend to be observed when estrogen hormones are at their lowest levels (i.e., pre-puberty [184] and post-menopause [162,172,181,183]). Estrogens have been shown to have a positive effect on blood vessel wall physiology through changes in the coagulation pathways [194], stimulating the production and release of nitric oxide [195], inhibition of proliferation of smooth muscle cells in arterial walls [196], and slowing the progression of atherosclerosis [197]. One hypothesis is that gender differences do exist due to an unfavorable influence shorter stature or smaller arteries on vascular function in females, however this is somewhat offset when estrogen is abundant (i.e., after puberty and before menopause).

Our findings suggest that neither male nor female adolescents are at increased risk of developing arterial stiffness. However, proper management of risk factors is vital to primary and secondary prevention of CVD, and there is substantial data showing that females are not at target levels of prevention. Female adolescents are at greater risk for developing CVD if they are inactive in their teenage years, but perhaps not at increased risk compared to males.

5.4 Predictors of Arterial Compliance

In the present study, it was found that systolic blood pressure, weight and shuttle run score (i.e. physical fitness) were predictors of both large and small arterial compliance. An inverse relationship between systolic blood pressure and arterial compliance is a logical finding since the force exerted by the blood against a vessel wall depends on not only the volume of blood contained within the vessels, but also on the compliance of the vessel walls.

From the Windkessel model, the energy and volume storage in the central blood vessels are dependent on an input pressure (stroke volume) and on the maintenance of system pressure by downstream resistance (systemic vascular resistance by the resistance arterioles) [198]. The first regression analysis supports the hypotheses that increased systemic vascular resistance is associated with decreased small artery compliance, and that increased stroke volume is associated with increased large artery compliance. When systolic and diastolic blood pressure and systemic vascular resistance are removed from the second regression analysis, stroke volume is still associated with an increase in large artery compliance. Athletes often demonstrate lower resting heart rates because an increase in size and contractility of the cardiac myocytes produces a higher stroke volume, therefore a lower heart rate is needed to maintain the same cardiac output.

Diastolic blood pressure was found to be a positive predictor of large artery compliance, which agrees with the premise that a widened pulse pressure reflects stiffness of the large arteries. Thus a more narrow pulse pressure (higher diastolic blood pressure), would increase large artery compliance, however, it is interesting to

find this in such a young population. It is known that pulse pressure increases with age from approximately age 50 years onwards because of opposing trends in systolic and diastolic pressure [199], causing increases in the size and work of the heart [60]. Increased pulse pressure has recently been recognized as an independent cardiovascular risk factor in middle-aged and older individuals [62,200], and has been suggested that it may improve the Framingham risk score [201].

Our results agree with previous studies that have examined predictors of vascular function in youth. Physical activity and physical fitness were positive independent predictors of endothelial function in children and adolescents age 9 to 14 years [106,107]. Trieber et al [107] additionally found systolic blood pressure to have a negative effect on endothelial function in adolescents. Predictors of large and small artery compliance also show similarities with other reports using diastolic pulse wave analysis in children and young adults [108,177]. Consistent with our findings, Reed et al [108] found shuttle run score and weight to be positive predictors, and systolic blood pressure to be a negative predictor of C2 in children between the ages of 9 and 12. Large artery compliance was also predicted by shuttle run score and systolic blood pressure, but in contrast to our findings, by height as well, with a positive effect. Arnett et al [177] also found that C1 could be negatively predicted by systolic blood pressure and positively by weight and in young adults (23 years). Similar to our findings, systolic blood pressure and weight were independent predictors of C2, however female gender and insulin levels were also found to have a negative effect.

Our finding that weight has a favorable effect on large and small arterial compliance is similar to one previous finding in children between the ages of 9 and 12

years of age [108]. Several studies have investigated the relation between body mass index and arterial compliance with contradictory results. In some studies, obese and overweight subjects have been found to have higher degrees of arterial stiffness and intima-media thickness [11,147,174,202-208], and in other studies lower degrees [108,177,209-211]. There are several possibilities for the paradoxical finding. The first possibility relates to whether the increase in arterial compliance is induced by the increase in arterial diameter seen in obese subjects [210]. However, obese subjects also have a marked increase in arterial distensibility [210], a measure of elasticity that is independent of initial vessel diameter. It is therefore likely that in overweight and obesity, an increase in arterial compliance does not result from an increase in arterial diameter.

An alteration in the concentration of vasodilating substances could be responsible for the paradoxical increase in arterial compliance with increases in body mass index. The secretion of nitric oxide might be increased in obesity because of the increase in blood volume, cardiac output, and peripheral blood flow, leading to an increase in vascular shear stress and subsequent increase in arterial compliance.

Another possibility is that the increase in arterial compliance may be due to cellular alterations of the arterial wall that are less resistant to vessel expansion, i.e. adipose cells and smooth muscle, which are more distensible than collagen [210].

Body fatness [212] and, in particular, central fatness [213-216] are major risk factors for cardiovascular disease. In contrast, peripheral fat has been shown to offer a protective effect on cardiovascular health as suggested by the observations that larger hip and thigh circumferences independently predict longevity in females [217]. The

Amsterdam Growth and Health Longitudinal Study [211] measured large artery compliance in 450 males and females beginning at age 13, and followed them for 23 years. They found that increased trunk fat was associated with decreased compliance of the carotid and femoral arteries, whereas increased peripheral fat was associated with increased compliance of the brachial artery and carotid-femoral segment. This suggests that the effects of body fat are not uniform along the arterial tree. Differences in metabolism of adipose tissue depending on whether it is located centrally or peripherally is proposed as one explanation. For example, higher lipoprotein lipase activity and lower fatty acid turnover in peripheral adipose tissue are more likely to take up free fatty acids from the circulation, which can result in impaired endothelial flow-mediated vasodilation [218]. Furthermore, Watts et al [147] showed although exercise training in obese adolescents was associated with significant improvements in aerobic capacity, strength and total body fat, the majority of fat lost was lost from the abdominal and trunk regions. Interestingly, subcutaneous fat did not change, even in these regions. Perhaps moderate amounts of peripheral body fat influence arterial structural and functional properties differently than other cardiovascular risk factors, and may in fact have a protective effect to a certain degree, similar to the observed "J"-shaped curve effect observed in which individuals with a low BMI demonstrate increased mortality, but not as high as that of obese and morbidly obese individuals [219,220]. Moreover, Flegal et al [221] recently showed that although underweight, obesity and very high levels of obesity were associated with increased mortality relative to the normal weight category (18.5 - <25 Kg/m^2), being overweight was not associated with excess mortality.

Finally, these paradoxical results may also be due to the different methods used to measure arterial compliance. For example, obese subjects are expected to have larger stroke volume and cardiac output simply because of the larger body size, and this could influence measures of arterial compliance (such diastolic pulse wave analysis) that rely on stroke volume for calculation. Similarly, the estimation of arterial length required of the pulse wave velocity measurements may not be accurate in obese individuals [222], and arterial compliance measurements using ultrasonography may be limited by decreased acoustic transmission in obese individuals [222].

5.5 Limitations of Investigation

A limitation of this investigation was that our subjects were volunteers. It is feasible that the parents and adolescents who volunteered to participate were more interested in physical fitness and predisposed to being active than those who did not participate. However, this does not impact negatively on the results found. The fact that shuttle run score was found to be an independent predictor of arterial compliance, even among a group of moderately active adolescents, suggests that risk factor modification in adolescence may be critical to prevent the onset of disease later in life. In addition, the total sample of the study from which this secondary analysis is based upon is 868 participants aged 5 to 19 from 14 schools, approximately one eighth of the total number of students enrolled in the Black Gold School District. According to previously published age- and sex-specific body mass indexes for children and adolescents aged 2 to 18 [223], 18.6% of the participants were overweight and 4.5% were obese. Janssen et al [224] recently showed that in a large cohort of Canadian youth between the ages of 11 and 16, 15.0% were overweight and 4.6% were obese, thus our

population is very similar. Our results of this secondary analysis in adolescents aged 13 to 17 are therefore likely generalizable to other adolescents.

Another limitation of this study was that pubertal status was not accounted for. Hormone levels are suspected to have an influence on vascular function. However, since gender differences in arterial compliance were not seen in our group of 13 to17 year-old adolescents after adjustment for differences in hemodynamic, anthropometric and fitness measurements, it is reasonable to assume that grouping males and females together to assess the impact of physical fitness on vascular function was not inappropriate.

Finally, the use of quartiles to classify the fitness level of the participants was another limitation. The quartiles do not represent distinct functional fitness levels and are somewhat artificial. Fitness quartiles were chosen for the design to add robustness to the analysis and provide a broader range of fitness levels for comparison. However, this design may not have been the most appropriate given the need for more participants in each quartile to detect a significant difference in arterial compliance.

5.6 Conclusion and Future Directions

The insidious process of atherosclerosis, that forms the basis for CVD, begins in early childhood. The endothelium plays a key role in the development of atherosclerosis, with injury to the endothelium cited as the primary causative factor. Structural and functional changes to the endothelium that line the arterial walls occur naturally with age, but also in response to disease. These changes can manifest though decreases in arterial compliance, and are heavily influenced by the persistence of CVD

risk factors. Moreover, arterial compliance has been shown to be a predictive tool of CVD risk.

The findings of this investigation demonstrate that adolescents with the lowest fitness levels had a 10% lower small artery compliance compared to adolescents with the highest fitness levels. Despite this difference not being statistically significant, physical fitness, as measured by a Legér shuttle run score, was an independent predictor of both large and small arterial compliance. The possibility that physical fitness influences arterial health is especially important, in light of recent reports that revealed decreasing levels of physical activity and increasing levels of obesity in childhood.

Body mass was found to be a positive predictor of large and small artery compliance. This paradoxical finding is difficult to explain, however emphasizes the importance of comprehensive assessment of body composition in future training studies. A higher body mass index clearly puts individuals at higher risk for CVD, however may not be detrimental to vascular function. Studies evaluating body mass index in lean, overweight and obese subjects are needed to assess a possible non-linear relationship between body mass index and arterial compliance.

Gender did not have an effect on arterial compliance in adolescents after adjustment for differences in anthropometric, hemodynamic and physical fitness measures. Most of the studies up to the present suggest a probable unfavorable influence of shorter stature on females causing increased vascular loading and decreased arterial compliance, however is somewhat offset after puberty and before menopause due to the presence of abundant estrogen. It is clear however, that the controversy regarding gender differences must be resolved for progress to be made in this important

field. Future studies comparing arterial compliance within genders of different heights may be useful to determine the true influence of height. Studies using multiple methods of measuring arterial compliance would also help to understand if differences in outcomes are due to different measurement techniques.

The extent of fatty streak lesions in the coronary vessels increases markedly in children and adolescents with multiple risk factors. This justifies the need to evaluate cardiovascular risk in young people and the effect of modifiable risk factors such as inactivity. Our finding that physical fitness (shuttle run score) is an independent predictor of both large and small artery compliance in a healthy adolescent population suggests that the beneficial associations between physical fitness and freedom from CVD begin early in life. This study provides support for the concept that vascular function is affected by physical inactivity, a modifiable risk factor, even at an early age. Teachers and parents of children and adolescents need to adopt the motto "hook them early" into acquiring positive physical activity patterns, not only for should the enjoyment, but for the many health benefits (including vascular health) and the carryover effect of early physical activity habits persisting into adulthood.

Future research should involve prospective studies in children to track arterial compliance and fitness into adulthood to determine the long-term impact of physical fitness in childhood, as well as studies assessing the ability of physical activity to effect arterial compliance independent of cardiorespiratory fitness. This will improve our understanding of how risk factors influence the course of CVD, and may also influence public health policy to promote active, physically fit children within the home, school and community environments.

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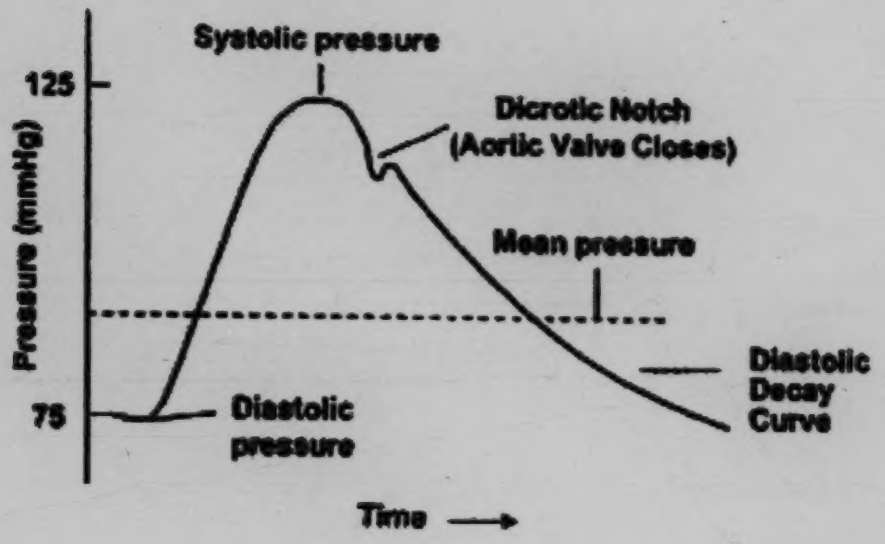
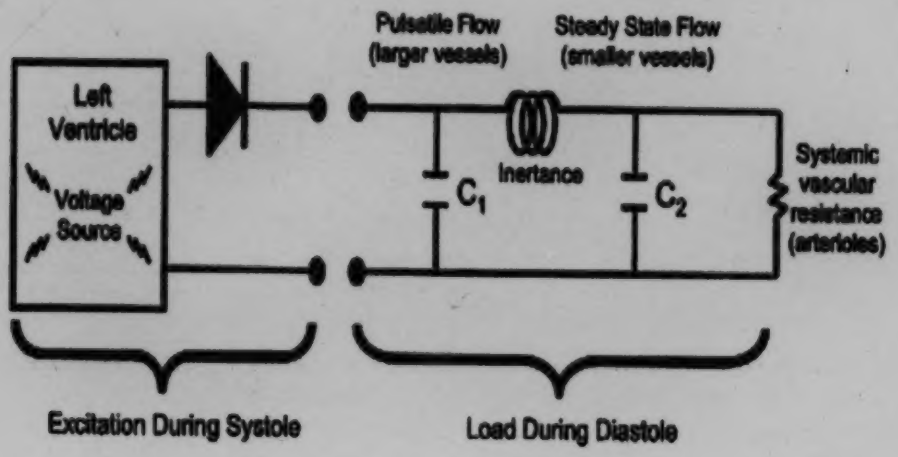
Appendix A – Blood Pressure Waveform

Reprinted with permission from Syeda et al, *Arterial compliance: a diagnostic marker for atherosclerotic plaque burden?* Am J Hypertens. 16;5: 356-62).



Appendix B. Electrical Schematic of the Modified Windkessel Model

Reprinted with permission from Cohn JN, *Arterial Compliance to stratify cardiovascular risk: more precision in therapeutic decision making.* Am J Hypertens, 2001, 14: 258S-263S.



Appendix C – Sample Size Calculation

From the unpublished observations of Reed et al [108], results for C2 between the second and fourth fitness quartile are:

$\mu_1 = 6.75$

$\mu_2 = 5.5$

Based on a review of the literature using CR-2000 to measure arterial compliance in both adults and children, standard deviation will be estimated at 2.3.

$\sigma = 2.3$

$$\frac{n}{\text{group}} = \frac{2(\sigma)^2}{(\mu 2 - \mu 1)^2} \times 7.9 \text{ [for alpha of 0.05 and beta of 80\%]}$$

$$= \frac{2(2.3)^2}{(1.25)^2} \times 7.9$$

$$= 54$$

Therefore, each quartile should contain 54 subjects.

Appendix D – Shuttle Run Speeds and Intervals According to Stage

Stage	Speed (km/h)	Interval (s)
1	8.0	9.0
2	9.0	8.0
3	9.5	7.6
4	10.0	7.2
5	10.5	6.9
6	11.0	6.6
7	11.5	6.3
8	12.0	6.0
9	12.5	5.8
10	13.0	5.5
11	13.5	5.3
12	14.0	5.1
13	14.5	5.0
14	15.0	4.8
15	15.5	4.7
16	16.0	4.5
17	16.5	4.4
18	17.0	4.2
19	17.5	4.1
20	18.0	4.0

Appendix E - Data Collection

School: _____

ID: _____

Age: _____

Gender: M ☐ F ☐

Height (cm): _____

Weight (kg): _____

Race: Caucasian ☐ Aisan ☐ African-American ☐ First Nations ☐
East Indian ☐ Pacific Islander ☐ Hispanic ☐

Shuttle Run Score: _____

Variable	T1	T2
Systolic Blood Pressure		
Diastolic Blood Pressure		
Mean Arterial Pressure		
Heart Rate		
Stroke Volume		
Systemic Vascular Resistance		
Total Vascular Impedance		
Cardiac Output		
Cardiac Index		
Large Artery Compliance (C1)		
Small Artery Compliance (C2)		
Signal Strength		

Appendix F - INFORMATION SHEET

(For Parents/Guardians)

Title of Project: Impact of body mass on insulin sensitivity and arterial compliance in children and adolescents

Clinical Investigators: Dr. Richard Lewanczuk
Dr. Lee Jones
Dr. Mark Haykowsky
Dr. Jon McGavock

PURPOSE: The purpose of this study is to assess blood vessel function and insulin sensitivity in children and adolescents.

BACKGROUND: Your child is being asked to participate in a study that will determine the impact of body weight on blood vessel function and insulin sensitivity. In adults, a relationship exists between body weight and the risk for heart disease and diabetes. Measuring blood vessel function and insulin sensitivity are important clinical tools to determine an adult's risk for developing these diseases. It now appears as though body mass may be related to blood vessel function and insulin sensitivity in children. Very little research has been done in children to this point, which is why we would like to measure blood vessel function and insulin sensitivity with a large number of children and adolescents (multi-year). We are also interested in the impact of physical activity on these variables, as increased physical activity patterns are associated with better health. Again, however, the impact of physical activity on blood vessel function and insulin sensitivity has yet to be studied in children and adolescents.

DESCRIPTION OF THE STUDY: All testing will be performed at your child's school under the guidance of graduate students and a nurse. The children will be tested on two separate occasions. The first day we will measure blood vessel function and insulin sensitivity, and the second day, we will measure your child's fitness, height, weight, hip and waist girth. We intend to perform these tests over a number of years to monitor possible changes in blood vessel function and insulin sensitivity.

Day 1: Blood vessel function will be measured using the machine depicted in the picture. This device is placed on the wrist over top of an artery that is close to the skin. **THIS TECHNIQUE IS COMPLETELY SAFE AND DOES NOT REQUIRE A NEEDLE OR ANY INVASIVE PROCEDURE.** This machine measures the pressure in your blood vessels for a period of 30 seconds and estimates how supple they are. To date, 71 children have been tested in the greater Vancouver area successfully and have shown that it is possible to use this machine in children and adolescents. This measurement is 100% safe and there are no risks associated with the measurement.

In this study, a new method of testing for the effect of insulin will be studied. This is a breath test that measures carbon-13 in the exhaled breath of your child. Your child will be given a small straw and asked to blow through the straw into a small tube for 4 to 8 seconds. He/she will then be given a sweet drink (100mL - about half a cup) that he/she will be asked to drink within five minutes. This drink will contain carbon-13 that will appear in the breath after approximately 90 minutes. Carbon-13 is not toxic and is completely safe. In this test, if insulin is working well, your child will breathe out carbon dioxide with carbon-13 in it. This is the same process that normally happens with the sugar you eat. If the insulin in your child's body is having trouble working, your child will not be able to break down glucose as quickly and less carbon-13 will be found in his/her breath. After drinking this drink, your child will be asked to return to class and sit quietly for 90 minutes. 90 minutes after taking the drink, your child will be asked to blow into a tube as before. If the results of this test indicate that your child has diabetes, we will advise you of this condition and set up an appointment with a physician to answer any questions you may have.

Day 2: On this day your child will be asked to run a shuttle run similar to an exercise that may have already been done as part of the physical education program. This test is designed to measure the physical performance levels of your child. Children will run in groups of 6-8 a distance of 30 meters, stop and run back to their original place. The pace at which they run will be controlled by a timed beep that we will play for them over a loud speaker or stereo system. The pace will begin very slowly and increase gradually, until your child is unable to maintain the cadence. After this test we will measure your child's height, weight, waist and hip girth.

This study is important to the medical and educational communities in Alberta and Canada, as it will provide valuable information about the cardiovascular and metabolic health of children and adolescents.

RISKS: There are no risks associated with any of the measurements being performed for this investigation.

CONFIDENTIALITY: Personal records relating to this study will be kept strictly confidential. Your child will never be identified by name in the study documents; rather we will track your child using their Alberta Education Student Number.